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TRANSIENT HYPERTROPHIC CARDIOMYOPATHY IN PREMATURE INFANTS

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The purpose of this study is to examine whether iatrogenic hypertrophic cardiomyopathy (HCM) in premature infants might be induced by routine neonatal therapies including the administration of hyperalimentation, dexamethasone, and/or insulin infusion. Infants with gestational age < 32 weeks and birth weight < 1250 grams were studied. Echocardiographic and metabolic analyses were performed before 48 hours of age at enrollment, and again at one, two, three, and five weeks thereafter.

Eleven patients were studied with a median gestational age of 26 weeks (range 24-29 weeks) and median birth weight of 804 grams (range 609-1230 grams). All eleven subjects received hyperalimentation, five received dexamethasone, and two received both dexamethasone and an exogenous insulin infusion. The ratio of interventricular septal to left ventricular posterior wall thickness increased significantly from 1.15±0.06 at enrollment to 1.51±0.06 ($p<0.05$) during the third week of life, consistent with the diagnosis of HCM. This ratio returned to a normal value of 1.17±0.1 by the fifth week of life. C-peptide excreted in the urine peaked during the fourth week of life at 253±99 μg/g creatinine, and a peak in circulating insulin levels to 19±4 μU/ml occurred during the third week of life. Both the excreted C-peptide and circulating insulin levels decreased by the end of the fifth week of life. All results are expressed as the mean±SEM.

This preliminary data suggest that the development of a transient hypertrophic cardiomyopathy occurs in premature infants, and appears to resolve as caloric intake, insulin production, and circulating insulin levels decrease.

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Introduction

Donald Teare was the first investigator to characterize the disease now known as Hypertrophic Cardiomyopathy (HCM).[1] In 1957, he described eight cases of asymmetrical hypertrophy of the myocardium, or what he termed "benign tumor of the heart", in a sub-group of people where sudden death and cardiac incapacity was rare. The eight cases he described occurred in men and women between the ages of 14 and 44. In three of the patients palpitation was the most striking early symptom that led to medical examination, and all three were found to have atrial fibrillation and some degree of heart failure. In addition, a history of "blackouts" was present in two cases. Interestingly, the macroscopic and microscopic features of the myocardium in all cases was virtually the same: the heart was marked by an overgrowth of muscle, particularly prominent in the interventricular septum, which impinged on the ventricular aspect of the mitral valve and lead to symptoms and signs of mitral stenosis. The pathological picture was one of bizarre and disorganized arrangement of muscle bundles associated with hypertrophy of individual muscle fibers and their nuclei, with varying degrees of fibrosis.[1]

Since Teare's initial description, the development of new technologies in the fields of cardiology, genetics, and endocrinology, has led to an even greater understanding of hypertrophic cardiomyopathy. HCM is now defined as a primary myocardial abnormality where left ventricular and/or right ventricular hypertrophy of unknown cause occurs.[2] Unlike the generalized and concentric cardiac muscle hypertrophy that occurs in response to an increase in afterload (such as in systemic hypertension or aortic valve stenosis), the hypertrophy in HCM is usually *asymmetrical*

and associated with microscopic evidence of myocardial fiber disarray.[2] In addition to the gross thickening of the ventricular wall, several histologic features have been identified in the myocardium, including cardiac muscle-cell disorganization, myocardial scarring, and abnormalities of the small intramural coronary arteries.[3]

In HCM, characteristically it is the left ventricle which is hypertrophied to a greater degree. The increase in left ventricular (LV) mass is due almost entirely to an increase in the thickness of the ventricular wall. Within the left ventricle, the distribution of hypertrophy is commonly also asymmetric and hypertrophy of the ventricular septum is by far the most common type of asymmetric hypertrophy.[2,3] The term asymmetric septal hypertrophy (ASH) was originally used by Teare to describe the gross pathologic appearance of the septum in patients with HCM.[1] ASH refers to the disproportionate hypertrophy of the septum compared to the posterior left ventricular wall.

One of the clinical and pathologic manifestations of ASH is known as Idiopathic Hypertrophic Subaortic Stenosis (IHSS). By definition, IHSS is a type of subaortic obstruction marked by the characteristic anatomic abnormality of asymmetric septal hypertrophy.[4] The pathology of subaortic obstruction is due to narrowing of the LV outflow tract as a result of ventricular septal hypertrophy and the anterior displacement of the papillary muscles and the anterior leaflet of the mitral valve.[2] As the myocardium contracts during systole, the mitral leaflets are "dragged" or pulled into the LV outflow tract. The leaflets collapse against the hypertrophied septum and cause obstruction to blood flow. This phenomenon is referred to as systolic anterior motion of the mitral valve leaflets. In this report, we will use the term HCM to refer to abnormal thickening

of the myocardium, particularly of the septum, which may or may not be associated with left ventricular outflow obstruction.

Transthoracic echocardiography and Doppler examination is undoubtedly the most important form of laboratory investigation in hypertrophic cardiomyopathy. These techniques can determine the location and extent of hypertrophy and the severity obstruction.[2] With echocardiography, asymmetric septal hypertrophy can be detected and is characterized by a ventricular septum that is thicker than the posterior wall of the left ventricle. Disproportionate ventricular hypertrophy in HCM is defined as the ratio of the interventricular septal thickness to that of the posterior wall of the left ventricle (IVS/LVPW) greater than 1.3:1[5] and/or demonstrating ventricular wall thickness greater than two standard deviations above the mean for gestational age[6]. (Normally the IVS/LVPW ratio approaches 1:1 in healthy subjects.[5]) The detection of ASH by cardiac echo represents the most specific and sensitive method available for diagnosing HCM.[4]

In addition to features of subaortic obstruction, diastolic dysfunction can also be a characteristic of HCM due to decreased ventricular chamber compliance. The disorganized and hypertrophied cardiac muscle cells lead to an increase in the stiffness of the ventricular chamber which impairs muscle relaxation and ventricular filling during diastole.[1] Furthermore, myocardial ischemia has been repeatedly demonstrated in HCM and may be related to small-vessel disease with decreased vasodilator capacity. Alternatively, it may be due to the increase in oxygen requirement needed to supply a large muscle mass.[2]

Clinical Course of HCM

HCM has been shown to occur in adults, children, and neonates. Asymmetric septal hypertrophy is the fundamental anatomic defect in HCM and its clinical spectrum ranges from asymptomatic persons, to symptomatic patients without outflow obstruction, and to severely limited patients with classical IHSS.[4]

The clinical course of HCM is variable, although the rate of progression of the disease is believed to be more rapid in children, adolescents, and young adults.[2] Left ventricular hypertrophy is not always fully expressed at birth and may change markedly in early life.[3,7] Importantly, the morphologic expression of HCM may not be complete, or even appear until childhood and adolescence, when body growth, development, and maturation are accelerated.[8] Patients with obstructive HCM typically complain of dyspnea, angina, and syncope on exertion. Congestive heart failure may be seen with severe obstruction to outflow or severe systolic and/or diastolic dysfunction.[2]

Sudden death is the most unpredictable and devastating complication of HCM and occurs most commonly in young patients. Data suggest that the most common precipitating factors of sudden death are cardiac arrhythmias, usually ventricular tachycardia.[2,3] Atrial and ventricular arrhythmias are an important feature of this disease and are associated with significant morbidity and mortality. The annual mortality in HCM is 4-6% in children and 3-4% in adults. HCM is the most common cause of unexplained sudden death in otherwise apparently healthy athletes.[2]

HCM can present clinically during infancy with congestive heart failure and cardiac enlargement, and can be a cause of infant death. In 1974, Maron studied the clinical features of HCM specifically in the infant population.[9] He described four infants

who each had marked hypertrophy of the ventricular septum which contained a disordered arrangement of hypertrophied cardiac muscle. He concluded that the characteristic pathologic feature of ASH in adults, a disproportionately thickened ventricular septum containing numerous hypertrophied and disorganized cardiac muscle cells, was present at birth.

In infants with HCM, unlike older children and adults with this condition, sudden death is less common than death due to progressive congestive heart failure.[10] Infants with HCM probably suffer from impairment of ventricular filling due to the increased number of cells and fibrosis of the myocardium, yielding a less compliant ventricle.[2,10] This results in diastolic dysfunction and impaired relaxation of the ventricular muscle. With higher filling pressures of the left ventricle and left atrium, pulmonary congestion may result. The ensuing tachypnea makes feeding difficult for the infant, and poor weight gain may result.

The Genetics of HCM

In adults, HCM is unusual among the primary cardiac diseases in that it frequently shows a familial pattern of inheritance. Genetic studies have demonstrated that HCM is often transmitted in a pattern consistent with an autosomal dominant trait with variable expression and penetrance.[3] Recent advances in the field of molecular genetics have led to the identification of the genes affected. At least 34 missense mutations have been described in the β-myosin heavy chain gene on chromosome 14.[2] In addition, mutations in the cardiac troponin-T and the α-tropomyosin genes have been described.[2] The hypertrophy in HCM may be compensatory in response to the abnormalities induced by

these mutations.[2] Echocardiographic studies have found that prevalence of the familial form in only about 50 percent of cases, while approximately 45 percent of the cases of HCM appear to be sporadic new mutations or may represent an acquired form of the disease.[3, 8]

In the pediatric setting, HCM can occur in one of two contexts. In children and adolescents it can be inherited as it is in the adult population. In neonates HCM also occurs even in those with no family history of HCM. In these latter cases it is hypothesized that the development of HCM may represent a new spontaneous mutation, or, more commonly, it may be secondary to exposure to an abnormal metabolic environment. Given the incidence of HCM in neonates without a family history of HCM, several hypotheses, other than a genetic defect, have been offered to explain the origin of the abnormal myocardial thickening observed in HCM. Investigators have suggested that hypertension, catecholamines, glucocorticoids, and/or hyperinsulinemia may play a causative role.[4]

HCM and Hyperinsulinemic States

Importantly, when HCM is discovered in infants, it must be distinguished from an etiologically distinct, transient, and non-familial condition occurring in infants diabetic mothers (IDM's). Like the genetic form of HCM, this condition is characterized by asymmetric septal hypertrophy, and may be associated with subaortic obstruction, and heart failure.[3] It is analogous to the adult form in that it can present with or without clinical symptoms. Like the adult form of HCM, arrhythmias and sudden death can occur. However, what is most distinct about this form of HCM seen in IDM's is that it is

transient and resolves within the first few months of life. It is proposed that the endogenous hyperinsulinemia induced in the infant of the diabetic mother produces *temporary* myocardial hypertrophy which may progress to a fatal obstructive cardiomyopathy.[11]

It is known that infants born to diabetic mothers have a propensity to develop cardiac disease. This high incidence of cardiovascular disease has been attributed to the abnormal metabolic environment and abnormal hemodynamics of the diabetic mother. However, a distinction must be made between the fetal abnormalities associated with gestational diabetes (White's Class A) and those associated with long-standing insulin dependent diabetes mellitus (such as White's Classes B, C, D, and E). (Refer to Appendix A for a description of White's Classification of diabetes in pregnancy.)

In a woman with previously diagnosed diabetes, maternal hyperglycemia occurs during the first trimester during embryogenesis. It is hypothesized that exposure of the first trimester embryo to abnormally high levels of glucose, as well as high levels of ketones and free oxygen radicals may act as teratogens. These infants are known to develop abnormalities of cardiovascular structure and anatomy, including complex heart disease such as the conotruncal defects (such as double outlet right ventricle, truncus arteriosus, tetralogy of Fallot) and other cardiac defects. In addition, these children are also at risk intra-uterine growth retardation due to placental vascular insufficiency, and for other congenital malformations such as anencephaly, spina bifida, caudal regression syndrome, absent kidneys, and tracheoesophageal fistula.

Alternatively, when hyperglycemia occurs in a woman with gestational diabetes, it is a third trimester phenomenon, long after organogenesis is completed. In these

fetuses, there is an association of hyperglycemia resulting in hyperinsulinemia, and consequently the development of myocardial hypertrophy. These fetuses do not have a high incidence of congenital abnormalities because they are not exposed to high levels of glucose and other potentially teratogenic substances during the critical period of organ formation in the first trimester.

The association of insulin excess with the development of HCM is well recognized.[11,12,13,14] Asymmetric septal hypertrophy was first observed in a stillborn infant of a diabetic mother by Maron et al in 1974.[9] In 1976, Gutgesell observed the typical hemodynamic and echocardiographic features of hypertrophic subaortic stenosis in three newborn infants.[12] Interestingly, in these patients the left ventricular obstruction resolved within the first six months of life. Family studies revealed no evidence of familial cardiomyopathy. However, the mothers of two infants had insulin-dependent diabetes mellitus and the mother of the third was presumed to be pre-diabetic, as evidenced by impaired glucose tolerance. We now recognize this as gestational diabetes mellitus.

Microscopically, the hypertrophic myocardial changes that have been noted in these infants include not only hypertrophy and hyperplasia of myofibrils but also disruption of the normal myofibrillar pattern, similar to that seen with familial HCM.[11] Subsequent investigators have confirmed that cardiac hypertrophy in the fetus and newborn of the diabetic mother is not an uncommon occurrence. Veille[6] examined 64 fetuses of diabetic mothers in utero and found that ventricular septal hypertrophy as defined by two standard deviations above the mean was present in 75% of these fetuses.

Sheehan[15] studied a series of 20 infants of well-controlled diabetic mothers and found that 35% exhibited exaggerated septal thickening.

In a second series of patients, Gutgesell examined the incidence and progression of this cardiomyopathy in 47 infants of diabetic mothers.[14] Twenty-four infants were symptomatic, five had marked septal hypertrophy with echocardiographic features suggesting left ventricular outflow obstruction, and one symptomatic infant died. These abnormalities resolved within the first six months of life and the echocardiograms in first-degree family members were normal. The results of this study confirmed that some infants of diabetic mothers are susceptible to a unique, apparently *transient*, form of hypertrophic cardiomyopathy. These results were also corroborated by Way in 1979 who studied the course of HCM in infants of diabetic mothers. He confirmed that the natural history is that of spontaneous regression of symptoms and septal hypertrophy.[5]

The echocardiographic, hemodynamic and histologic features of HCM in infants of diabetic mothers are similar to those of familial HCM. However, the tendency for the echocardiographic abnormalities to disappear within the first six months of life is unlike the natural history of other forms of HCM. The lack of asymmetric septal hypertrophy in family members, and the tendency for the hypertrophy to decrease with time indicate that the cardiomyopathy of IDM's has a different etiology than familial HCM.

Gutgesell hypothesized that the cardiac hypertrophy of IDM's could represent another manifestation of their generalized organomegaly since these infants become macrosomic as the excess glucose that passes transplacentally is deposited under the influence of excess fetal insulin.[14] In addition, he proposed that fetal hyperinsulinemia

would promote increased glycogen, lipid, and protein synthesis, with resultant obesity and macrosomia.

For infants of diabetic mothers, there is a direct association between hyperinsulinemia and macrosomia.[13] It is known that blood glucose freely crosses the placenta by facilitated diffusion, and therefore, fetal blood glucose reflects maternal blood glucose levels. By this mechanism, chronic maternal hyperglycemia directly results in fetal hyperglycemia. As elevation of blood glucose induces insulin secretion, a small increase in maternal blood glucose may affect fetal pancreatic beta islet growth, leading to fetal hyperinsulinemia. This is known as the *Hyperglycemic Hypothesis* which proposes that the infants' pancreatic islets grow and secrete more insulin because they are stimulated by small increments of blood glucose.[16]

Hypertrophy and hyperplasia of fetal islets as well as an increased content and secretion of insulin are well documented in infants of diabetic mothers. Steinke looked at the insulin content of the pancreas from fetuses and infants of diabetic mothers.[16] He found that the pancreases of the offspring of diabetic mothers contained more insulin than the corresponding control group. Seven of the nine pancreases from the IDM's showed typical marked hypertrophy and hyperplasia of the pancreatic islets. The insulin content of fetal pancreases from infants of diabetic mothers as a group was markedly elevated. The increased insulin content correlated with the histological picture of islet hypertrophy and hyperplasia observed in infants of diabetic mothers. His results favor the hyperglycemic hypothesis.

It has been shown that insulin has an important role specifically in the developing fetal heart. James Steven demonstrated that plasma membranes of neonatal human and

guinea pig myocardium are rich in insulin receptors.[17] It is known that insulin plays a significant role in fetal metabolism and growth by regulating glycogen, fat, and protein synthesis which is responsible for the marked fetal growth during the third trimester. It was initially believed that the increase in fetal insulin, in association with the high number of insulin receptor sites led to increased protein, glycogen, and fat synthesis and subsequent hyperplasia and hypertrophy of myocardial cells observed in large infants of diabetic mothers. However, subsequent post-mortem studies in IDM's have demonstrated that the myocardium is marked by a disorganized arrangement of cells along with hyperplasia and fibrosis. It is not known how insulin influences the myocardium to undergo these abnormal cellular changes. The sensitivity of the myocardium to insulin is also supported by the fact that the cardiomegaly in the IDM's is disproportionate to the enlargement of the other organs.[18]

Breitweser hypothesized that fetal hyperinsulinemia contributes *directly* to the septal hypertrophy and demonstrated that as the serum insulin level and number of insulin receptors decrease following birth, septal hypertrophy regresses.[19] In another study, Nehgme examined the mechanism of HCM in infants of diabetic mothers. He demonstrated a direct effect of insulin on cell growth and division in cultured neonatal rat ventricular myocytes manifested by increased cell surface area, protein content, and protein synthesis.[20] These observations suggest that fetal hyperinsulinemia is responsible for HCM in the infant of the diabetic mother.

In addition to infants of diabetic mothers, other hyperinsulinemic, insulin-sensitive states have been associated with excessive growth of cardiac muscle. For example, infants with nesidioblastosis who have ductuloinsular cell proliferation with

hyperplasia of the pancreatic islets can develop features of HCM.[13] Insulin-induced cardiomyopathy has also been described in beta cell adenoma.[11] Additionally, HCM has also been noted in a number of insulin-resistant states. Children with leprechaunism who have massive hyperinsulinemia, with insulin levels as much as one-hundred times normal, have also been found to develop HCM.[13] This condition results from a genetic mutation that affects the number of function of insulin receptors. However, IGF-1 receptors are structurally homologous to insulin receptors which may provide the mechanism by which insulin could continue to promote tissue-specific growth of the heart. Other insulin-resistant hyperinsulinemic disorders associated with ventricular septal hypertrophy include lipodystrophy, acromegaly, and hypothyroidism.[13]

Dexamethasone and the Development of HCM

The association of HCM with excess exposure to glucocorticoid is also well established.[11,20,21] Dexamethasone has been used in the treatment of ventilator-dependent infants with bronchopulmonary dysplasia (BPD) to accelerate weaning from artificial ventilation and to reduce pulmonary complications. The well-known side effects include suppression of the hypothalamic-pituitary-adrenal axis, hypertension, catabolism, and perforated gastrointestinal ulcers.

In 1993, Brand et al reported the occurrence of HCM in an another unexpected population. The authors reported three infants who developed hypertrophic obstructive cardiomyopathy during dexamethasone treatment for bronchopulmonary dysplasia.[21] The Doppler tracings demonstrated muscular sub-valvular obstruction with a significant pressure gradient in the left ventricular outflow tract. After discontinuation of

dexamethasone therapy, septal and left posterior wall thickness decreased to normal. Because the hypertrophic obstructive cardiomyopathy appeared and progressed during dexamethasone therapy and resolved completely after its cessation. A causative association between the hypertrophic cardiomyopathy and the exogenous glucocorticoid therapy was inferred.

Since dexamethasone has no mineralocorticoid potency, a glucocorticoid effect is proposed to be responsible for the development of HCM. Glucocorticoids decrease peripheral glucose utilization and stimulate gluconeogenesis, thus causing hyperglycemia and reactive hyperinsulinemia. A reduced sensitivity to insulin-mediated cellular glucose uptake leads to a rise in plasma glucose and hence to a compensatory stimulation on insulin secretion in an attempt to normalize plasma glucose. Thus increasing insulin resistance elicits a progressive rise in circulating insulin. Overt fasting hyperglycemia finally develops when insulin resistance is severe and the compensatory insulin response is exhausted.[22] The anabolic properties of insulin could induce cardiac muscle hypertrophy as has been described in the infants of diabetic mothers.

Werner also evaluated the potential induction of cardiac effects by high-dose dexamethasone therapy.[23] Again, the therapy was associated with a significant increase in the thickness of the interventricular septum, diastolic left ventricular free wall, and diastolic right ventricular free wall. These effects were transient, reached their maximal degree by the third week of treatment, and approached pre-treatment conditions by the sixth week of treatment. He concluded that a transient absolute myocardial hypertrophy was associated with dexamethasone therapy in infants with bronchopulmonary dysplasia.[23]

However, the relationship of HCM to infants with BPD is further complicated. It has been suggested that the onset of HCM could be related to the BPD itself, rather than simply due to the effects of a particular metabolic environment. Left ventricular hypertrophy is occasionally observed in infants with BPD, possibly due to increased catecholamine synthesis as a result of recurrent hypoxemia.[24] However, in Brand's study, the clinical and radiologic signs of BPD remained in the patients after the HCM had resolved completely, making a causal association unlikely.[21]

In addition, arterial hypertension is a common side effect of glucocorticoids. Hypertension, if present, could play an important role in the pathogenesis of HCM.[24,25] Glucocorticoids have been associated with increased peripheral vascular resistance and with diminished activity of vasodilating prostaglandins. However, Brand's patients had normal blood pressure measurements throughout the course of dexamethasone.[21] On the other hand, Werner demonstrated that there was a transient increase in the heart rate and mean arterial blood pressure of the infants treated with dexamethasone.[23] However, systemic hypertension is unlikely to be the sole cause of the myocardial hypertrophy observed because the degree of hypertrophy was out of proportion to the extent of elevation of mean arterial pressure. In addition, Brand's infants had hypertrophy of both the left and right ventricle, rather than isolated left ventricular hypertrophy, which indicates that systemic hypertension unlikely as the sole cause of their observed HCM.[21]

Preliminary Data at Yale-New Haven Children's Hospital

In 1995, the pediatric cardiology service at Yale-New Haven Children's Hospital was consulted to evaluate two very-low-birth-weight premature infants for the presence

of a patent ductus arteriosus. The initial echocardiographic assessment showed no evidence of heart disease whatsoever, including normal myocardial wall thickness and chamber dimensions. However, two weeks later, they were re-evaluated due to the presence of newly recognized systolic heart murmurs. One of these patients had symptoms of congestive heart failure. In both infants, the second echocardiogram demonstrated the development of severe HCM with significant thickening of the septal and ventricular walls. The infant with congestive heart failure had evidence of subaortic obstruction. Neither infant had a family history of HCM, nor were their mothers diabetic during pregnancy. While exploring plausible etiologies, it was noted that the infants had received high-calorie total parenteral nutrition (TPN) and had been on chronic insulin infusion because they had been unable to maintain normal serum glucose levels. In addition, one of these infants had received dexamethasone as therapy for chronic lung disease.

As demonstrated in these two patients, standard medical management of the premature infant often includes hyperalimentation to maximize caloric intake and promote somatic growth. Exogenous insulin infusion may be required to maintain euglycemia. In addition, dexamethasone therapy is frequently used to wean ventilatory requirements and prevent chronic lung disease and which is common in premature infants. The question posed was whether these therapies could be responsible for a *post-natal* environment characterized by elevated insulin levels. This would produce a metabolic environment similar to that of the fetus of the diabetic mother and would lead to the development of HCM.

Statement of Purpose:

Based on established data and the preliminary data observed at Yale New-Haven Children's Hospital, we proposed that routine management of the premature infant, including high dose total parenteral nutrition, exogenous insulin infusion, and dexamethasone therapy, could produce a metabolic environment characterized by hyperinsulinemia. *We hypothesized that hyperinsulinemia in the premature infant may lead to the development of hypertrophic cardiomyopathy. We further hypothesized that normalizing the hyperinsulinemia will result in the resolution of HCM in the premature infant.*

We designed a prospective experimental study in which all premature infants with birth weights less than 1250 grams would receive metabolic and cardiovascular evaluation before, during, and after routing neonatal management strategies are undertaken.

The specific aims of this study were:

1. To quantify the circulating insulin levels during the first six weeks of life in the premature infant who may be receiving hyperalimentation and/or insulin and/or dexamethasone therapy.
2. To quantify ventricular structure, mass, systolic and diastolic function and wall stress during the first six weeks of life in the premature infant who may be receiving hyperalimentation and/or insulin and/or dexamethasone therapy.
3. To evaluate the relationship between glucose dosage, dexamethasone dosage, insulin dosage, circulating insulin levels and the development and/or severity of HCM in the premature infant.

Methods

Enrollment of Subjects

Inclusion criteria for study subjects included all premature infants admitted to the Yale-New Haven Children's Hospital Newborn Special Care Unit with a gestational age no greater than 32 weeks and a birth weight of 1250 grams or less. The infants were enrolled within 48 hours following birth. Exclusion criteria included any congenital heart disease other than normal fetal shunting pathways, such as patent ductus arteriosus and patent foramen ovale. Infants with evidence of endocrinologic disease and infants born to mothers with gestational or pre-gestational diabetes mellitus were also excluded.

Overview of Study Protocol

The length enrollment for each subject in the study was five weeks, or 35 days. The study protocol included daily assessment of the subject's growth parameters, blood pressure, caloric intake, types of feedings, medications, respiratory management, and daily measurement of blood glucose by finger-stick technique. Interval assessment of serum insulin levels as well as urinary C-peptide levels, were obtained on Days 0 (enrollment), 7, 14, 21, and 35. In addition, complete bedside echocardiographic assessment was performed on study Days 0, 7, 14, 21, and 35.

Measurements

The data for this study was obtained in a prospective observational manner.

Maternal Parameters: At the time of enrollment, the study subject's mother was interviewed by the research assistant in order to assess the pregnancy and birth history.

Data collected included maternal age, gestational history, past medical history, significant family medical history, and the use of any medications during the course pregnancy, specifically glucocorticoids and beta agonists. In addition, the mother's metabolic history during gestation was obtained, including the results of any glucose tolerance tests. A Hemoglobin A1c level was analyzed immediately following enrollment as an indicator of maternal glucose balance during the last three months of pregnancy.

Subject Data: At the time of enrollment, the subject's birth history was reviewed by the research assistant, including Apgar scores, birth weight, body length, head circumference, and assessments of gestational age by the estimated date of confinement and by the physical exam. The administration of exogenous surfactant, if any, was noted.

Clinical Parameters: Detailed clinical monitoring and medical record review was conducted and tabulated by the research assistant on a daily basis throughout the course of the study. The parameters assessed included the subject's weight, heart rate, respiratory rate, and blood pressure. The subject's ventilatory status was recorded, including type of assisted mechanical ventilation, inspired oxygen concentration, and arterial oxygen saturation. The volume and type of intravenous fluids administered was recorded, with calculation of total calories provided over 24 hours, as well as the concentration of glucose, lipids, and protein in the hyperalimentation solution. All drug treatments were recorded, including the dose and number days of therapy of insulin infusion and/or dexamethasone therapy.

Metabolic Parameters: At enrollment (Day 0) and on days 7, 14, 21, and 35, a 0.5 cc sample of blood was obtained from the subject and measured for glucose and

insulin. A urine sample was obtained to analyze the urinary excretion of C-peptide, a byproduct of insulin metabolism.

Echocardiographic Evaluation: Each subject underwent a baseline echocardiogram at enrollment, consisting of two-dimensional real-time imaging as well as M-mode assessment, pulsed Doppler analysis and color Doppler mapping of flow patterns. The investigator performing the evaluation was blinded as to the metabolic and respiratory therapy provided to the subject. The echocardiographic parameters were measured again throughout the course of the study on days 7, 14, 21, and 35 following enrollment.

Specifically, the echocardiogram focused on measuring ventricular wall thickness, the cavity dimensions of the left ventricle, and the flow dynamics of the left ventricle across the mitral valve. The left ventricular mass, as well as the wall stress of the left ventricle, was measured by standard two-dimensional and M-mode techniques. Other indices of ventricular systolic function such as ejection fraction, shortening fraction as well as indices of diastolic function such as peak E and A velocity, E to A ratio, and isovolumetric relaxation time were measured and recorded. Doppler analysis was performed to determine the presence and severity of obstruction to left ventricular outflow, and to determine the stoke volume and the cardiac output in these patients. Finally, color flow mapping was used to detect the presence of shunting at the level of the ductus arteriosus and/or foramen ovale. (Refer to Appendix B for further definition of the echocardiographic parameters measured in this study and the formulas used for calculations.)

Data Analysis: Statistical analysis was performed using ANOVA when comparison of repeated measures over time were made. In addition, correlation coefficients and multivariate analysis were performed. Since all premature infants by definition are not healthy and are exposed to a variety of nutritional and medical therapies, there were no "normal" controls. Therefore, subjects served as their own controls, with the baseline values obtained at enrollment serving as control values. When comparisons were made between subject groups, the Kruskal-Wallis test was used. Measurements of cardiac structure and function were compared to normal values as reported in the literature. Results are reported as the mean ± the standard error of the mean unless otherwise stated.

Results

From July 1996 through June 1997, fifteen patients were enrolled for the study from the New Born Special Care Unit at Yale-New Haven Children's Hospital. However, two infants were transferred out of Yale-New Haven Children's Hospital and two died before the end of the study protocol. Table 1 shows the characteristics of the subjects who participated in the study. A total of eleven patients completed the protocol (3 male and 8 female) with a median birth weight of 804 grams (range of 609-1230 grams) and median gestational age of 26 weeks (range of 24-30 weeks). Three of the mothers received perinatal steroids.

As a group, the infants in the study became relatively hyperinsulinemic by Day 14 of the study compared to baseline. Figure 1 shows that serum insulin levels increased significantly from a baseline of 14.6±2.5 μU/ml to 18.3±3.1 μU/ml ($p<0.05$) by the end of the second week of life. Resolution of the hyperinsulinemia occurred by Day 21, as insulin levels returned to baseline and remained normalized until the end of the study protocol. This suggests a relative hyperinsulinemia during the second to third weeks of life. We also analyzed urinary C-peptide levels, in order to further assess the infants' endogenous insulin production. Figure 2 shows a similar statistically significant increase in the excreted urinary C-peptide from 127 ± 33 μg/g creatinine on Day 0 to 242 ± 71 μg/g creatinine ($p < 0.05$) on Day 21. The peak in urinary C-peptide levels occurred one week after the insulin peak.

Figure 3 demonstrates that for the group as a whole, there was a significant increase in the ratio of the interventricular septal thickness to left ventricular posterior wall thickness (IVS/LVPW) from a baseline value of 1.18 ± 0.06 to 1.37 ± 0.07 by Day 14 of the protocol ($p < 0.05$). As a group, the infants met the criteria for the diagnosis of

HCM, with an IVS/LVPW ratio >1.3:1. The development of HCM was transient, and resolved by Day 21. These hypertrophic changes and their resolution correspond to the hyperinsulinemia and its resolution.

However, not all of the subjects enrolled developed echocardiographic evidence of HCM. We then compared those subjects who developed HCM to those subjects who did not develop the disease. Both groups had a normal IVS/LVPW ratio at enrollment, however, seven of the eleven (64%) subjects had an IVS/LVPW ratio of 1.51:1 during the second week of life as is shown in Figure 4, meeting diagnostic criteria for HCM. One of these subjects had symptoms of congestive heart failure, while the other six were asymptomatic. In the HCM subgroup, the ratio returned to normal by the third week of life, indicating the resolution of HCM.

Figure 5 is an M-mode echocardiogram performed at enrollment (age 3 days). The image reveals normal septal and posterior wall thickness and a normal IVS/LVPW ratio. In contrast, Figure 6 demonstrates the marked hypertrophy of the septum without concomitant change in the posterior wall, yielding a highly abnormal IVS/LVPW ratio. This image representing HCM was obtained during the second week of life.

Interestingly, both groups of patients, those with HCM and those without HCM, developed a relative hyperinsulinemia during the second week of life to levels of 19.9 ± 4.4 and 17.0 ± 4.8, respectively, as shown in Figure 7. However, there was no statistical difference in the peak serum insulin levels between the two groups.

Several differences were noted when comparing the subjects who developed HCM to those that did not. Table 2 shows that the subjects that were smallest and most immature were those that did not tend to develop HCM. The subjects who developed HCM tended to be gestationally more mature than those subjects who did not develop

cardiac hypertrophy, with a mean gestational age of 27 ± 0.8 weeks versus 25 ± 0.4 weeks ($p = 0.07$). In addition, subjects with HCM had a mean birth weight of 868 ± 66 grams compared to 690 ± 50 grams ($p = 0.10$) in those who did not develop HCM. Although these numbers were not statistically significant, they did show a trend toward significance.

Therapies also differed among the subjects. While all subjects received nutrition via hyperalimentation during the course of the study, two (18%) received dexamethasone for chronic lung disease as well as exogenous insulin infusion for persistent hyperglycemia. Five subjects (45%) received hyperalimentation and dexamethasone, and four subjects (36%) received hyperalimentation alone. As the subject groups were broken down by types of therapies received (ie hyperalimentation, exogenous insulin, and/or dexamethasone), we looked at the percent change in thickness of the ventricular septum from baseline. Figure 8 shows that although all three treatment groups demonstrate a relative increase in myocardial thickness during week 2, the greatest increase in IVS/LVPW thickness ratio occurred in the group of patients who received hyperalimentation alone, from a baseline IVS/LVPW ratio of 1.04 ± 0.78 at enrollment to 1.51 ± 0.10 by Day 14 of life. This was followed by those who received both hyperalimentation and dexamethasone (peak IVS/LVPW ratio of 1.20 ± 0.10 at Day 14) The smallest change in septal hypertrophy occurred in subjects who received all three therapies (IVS/LVPW ratio of 1.33 ± 0.12 at Day 14).

We also looked at the change in serum insulin levels based on the number and types of therapies the study subjects received in the neonatal intensive care unit. Figure 9 shows that although all three groups had a relative increase in serum insulin levels at week 2 over baseline at enrollment, the highest serum insulin levels were measured in the

babies who received all three therapies. These infants had an increase in serum insulin from 20.00 ± 6.50 at baseline to a peak of 29.50 ± 0.50 at Day 14. The subjects who received both hyperalimentation and dexamethasone and subjects who received hyperalimentation alone had insulin levels which were lower during the second week of life (peak insulin levels of 15.25 ± 4.88 and 29.50 ± 0.50, respectively).

In order to assess myocardial function in patients with and without HCM, we analyzed the ejection fraction and myocardial circumferential shortening fraction as measured by bedside transthoracic echocardiography (See Appendix B). Table 3 shows the trend in ejection fraction (EF), a measure of global systolic performance, during the course of the study for both normal subjects and those who developed HCM. The values for the EF at each stage of the study protocol were within normal limits (0.55-0.80) and without much variability. In addition, neither group was significantly different from the other. Table 4 shows the trend in circumferential shortening fraction. Again, in both groups of subjects the circumferential shortening fraction remained within normal limits throughout the course of the study (0.29-0.44), and the groups did not differ significantly from each other.

Some prior studies have suggested that the use of dexamethasone in the treatment of chronic lung disease in premature infants can cause systemic hypertension [24,25]. We measured daily blood pressured in all study subjects. No significant hypertension was seen. In fact, only one infant had a blood pressure of 90 mm Hg at one isolated measurement. All measurements for all other subjects were within normal limits (considered to be a systolic pressure <90 mm Hg in the New Born Special Care Unit at Yale-New Haven Children's Hospital). The data are shown in Figure 10. There was no statistical significance in the blood pressures measured between the two groups.

Table 1: Subject Characteristics

Subjects	Gender	Birth Weight (gms)	Gestational Age (wks)	Maternal Perinatal Steroids
11 completed protocol	3 male 8 female	804 (median) 609-1230 (range)	26 (median) 24-30 (range)	3 mothers received one dose within 24 hours of delivery

Table 2: HCM Subgroup Characteristics

Subgroup	Number of Subjects	Gender (m:f)	Birth Weight (grams)	Gestational Age (weeks)
HCM	7	3:4	830 (median) 700-1230 (range)	27 (median) 25-30 (range)
No HCM	4	0:4	663 (median) 609-825 (range)	25 (median) 24-26 (range)

Figure 1: Insulin Levels

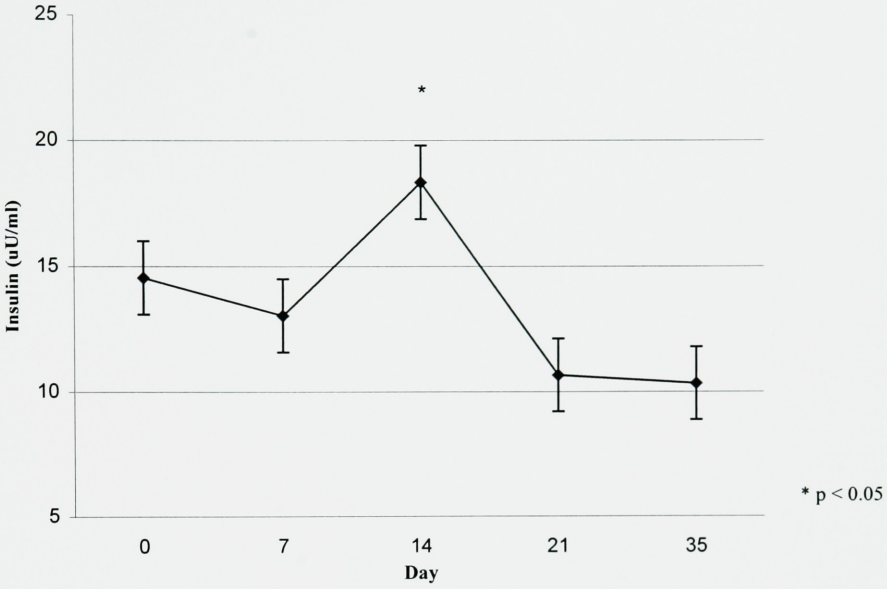

Figure 1: Serum insulin levels increased significantly by the end of the second week of life to levels that were higher than at enrollment and than at three and five weeks of life (study days 21 and 35, respectively)

Figure 2: Urine C-Peptide

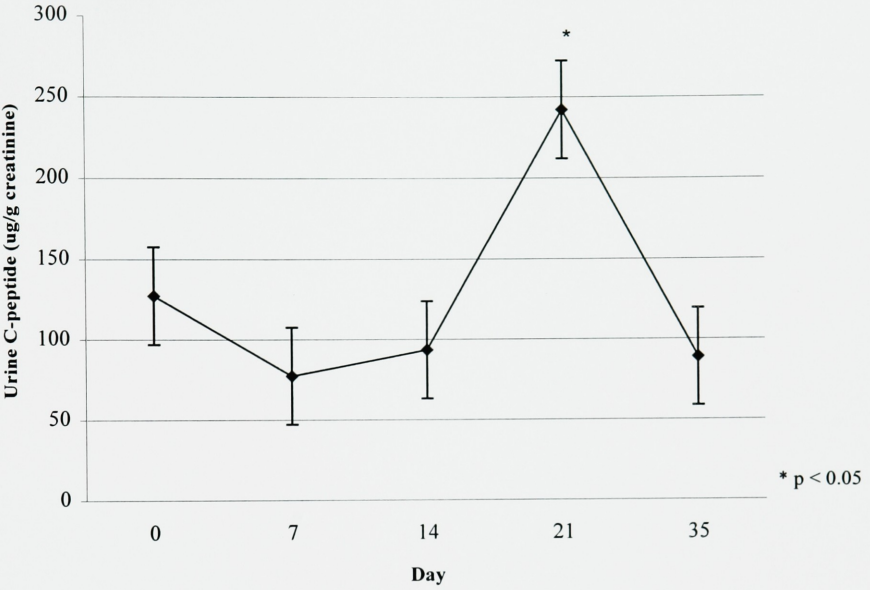

Figure 2: Excreted urinary C-peptide, a marker of endogenous insulin production, increased by the end of the third week of life (Day 21). The levels at Day 21 were significantly higher than at enrollment and than at Day 35 of the study.

Figure 3: IVS/LVPW Ratio

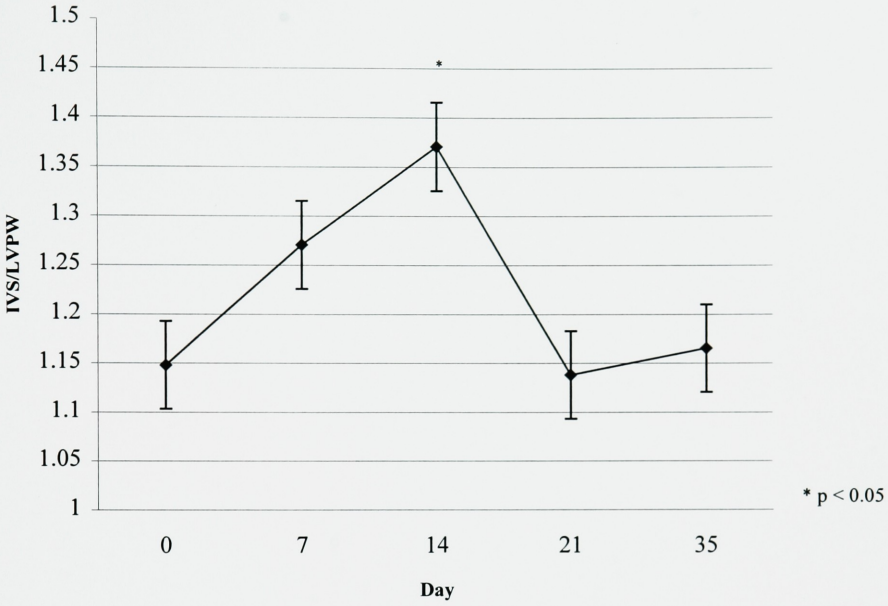

Figure 3: There was a significant increase in the IVS/LVPW thickness ratio by the end of the second week of life to a level that exceeded normal, meeting the diagnosis of HCM. This hypertrophy resolved by the third to fifth weeks of life.

Figure 4: IVS/LVPW Ratio by Subgroup

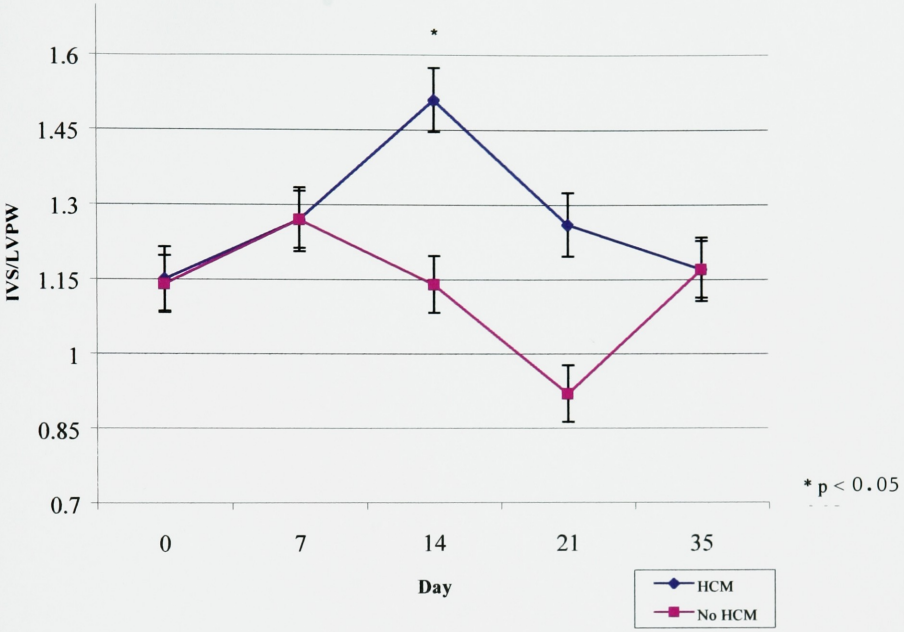

Figure 4: Not all premature infants developed HCM. The subjects who developed HCM had marked hypertrophic changes by the second week of life. This hypertrophy resolved by the third and fifth weeks of life.

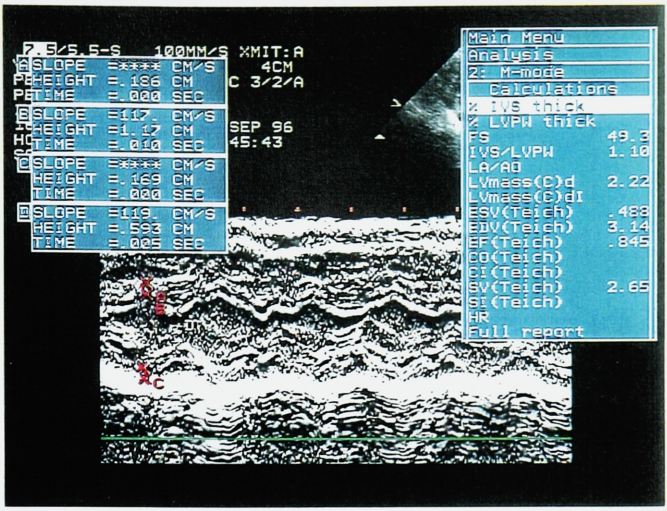

Figure 5: This is a representative M-mode echocardiogram from a subject at enrollment, where A marks the thickness of the interventricular septum, B marks the dimensions of the left ventricle, and C represents the thickness of the left ventricular posterior wall. In this patient the interventricular septum measures 0.186 cm and the left ventricular posterior wall measures 0.169 cm, with a normal IVS/LVPW of 1.10.

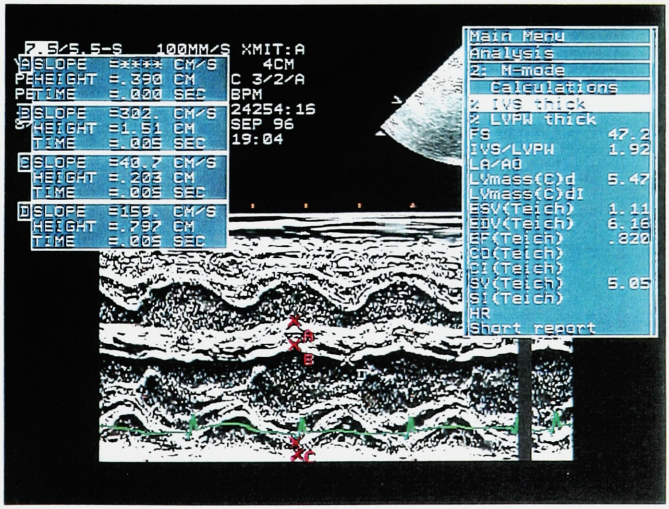

Figure 6: This is an M-mode echocardiogram a patient with HCM performed during the second week of life. The interventricular septum measures 0.390 cm and the posterior wall measures 0.203, with an abnormal IVS/LVPW of 1.92.

Figure 7: Insulin Levels by Subgroup

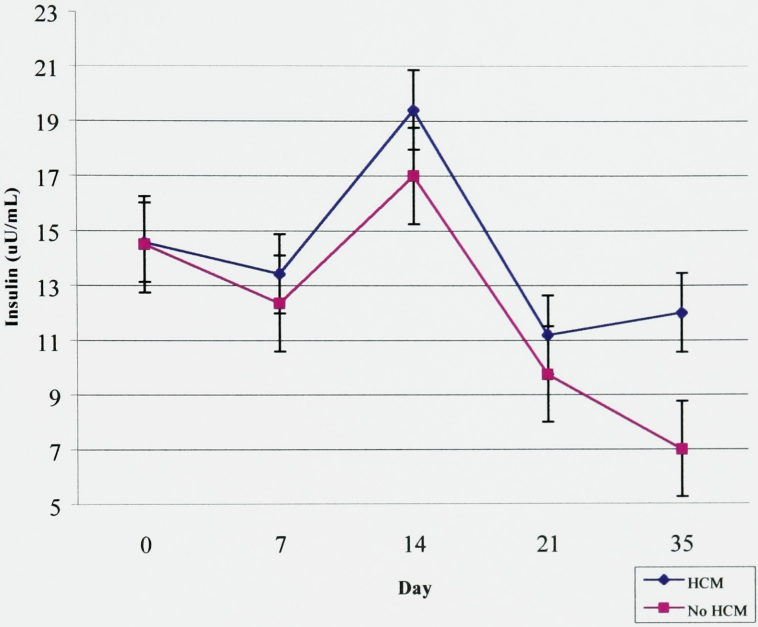

Figure 7: Both groups of subjects, those with HCM and those without HCM appear to have a similar relative hyperinsulinemia during the second week of life.

Figure 8: IVS/LVPW by Therapies Received

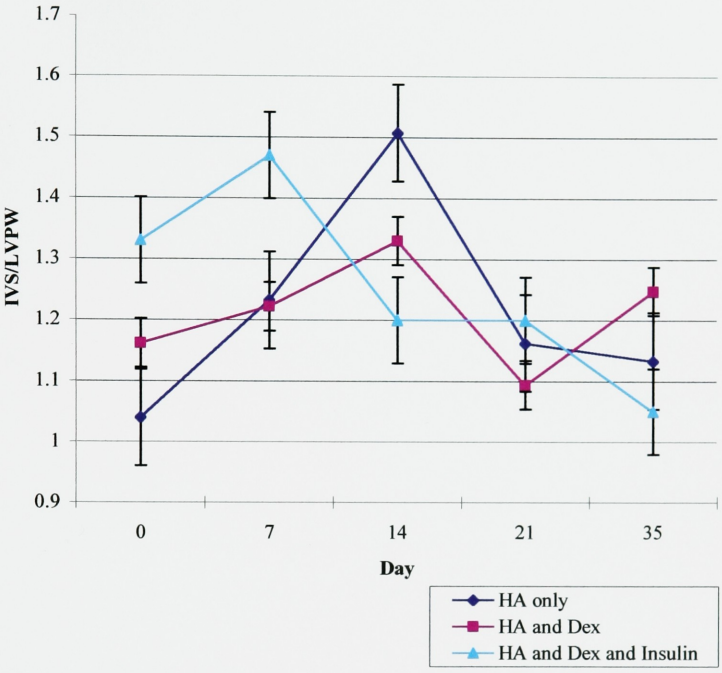

Figure 8: When broken down by types of therapies received, the greatest increase in myocardial thickness from baseline occurred in the infants who received hyperalimentation alone, followed by those infants who received both hyperalimentation and dexamethasone. The smallest change in septal thickness occurred in subjects who received all three therapies.

Figure 9: Insulin Levels by Types of Therapies Received

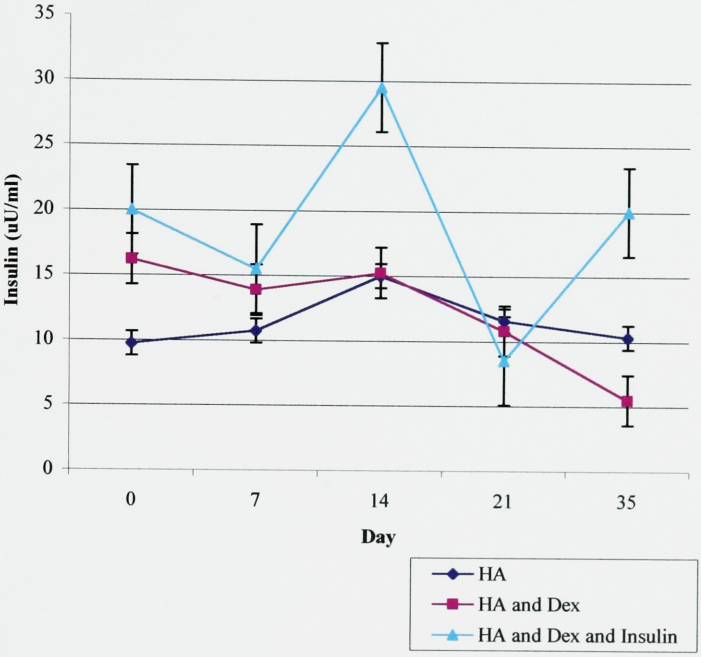

Figure 9: During week 2 of life, the highest peak levels of insulin were measured in the infants who received all three therapies. The subjects who received both hyperalimentation and dexamethasone and subjects who received hyperalimentation alone had lower peak insulin levels during the second week of life.

Table #3: Ejection Fraction in Subjects With and Without HCM

Study Day #	HCM (n = 7)	No HCM (n = 4)
0	0.68 ± 0.03	0.71 ± 0.04
7	0.77 ± 0.03	0.80 ± 0.04
14	0.81 ± 0.03	0.79 ± 0.03
21	0.77 ± 0.03	0.78 ± 0.03
35	0.78 ± 0.03	0.77 ± 0.02

Table #4: Circumferential Shortening Fraction in Subjects With and Without HCM

Study Day #	HCM (n = 7)	No HCM (n = 4)
0	0.35 ± 0.02	0.36 ± 0.03
7	0.42 ± 0.02	0.46 ± 0.05
14	0.47 ± 0.03	0.45 ± 0.03
21	0.43 ± 0.03	0.43 ± 0.03
35	0.44 ± 0.02	0.41 ± 0.02

Figure 10: Sytolic Blood Pressure

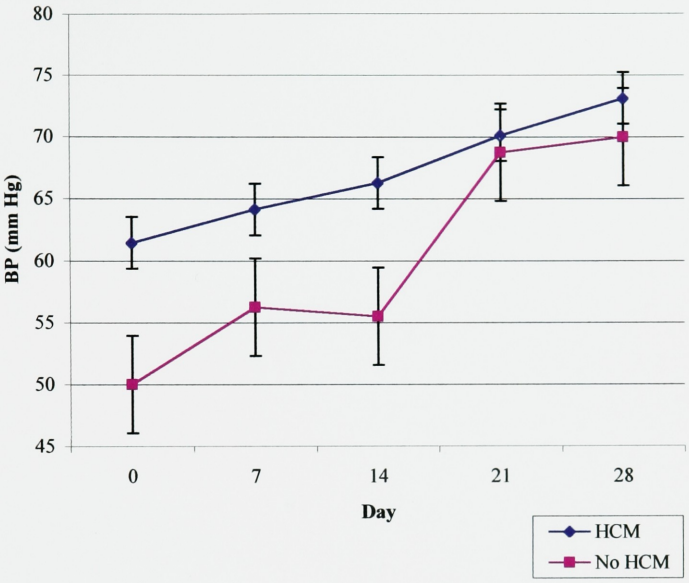

Figure 10: In both groups of subjects, those with HCM and those without, the systolic blood pressures remained less than 75 mm Hg throughout the duration of the study, demonstrating that as a group these infants did not develop systemic hypertension.

Discussion

Our study results demonstrate that premature infants are at significant risk for developing hypertrophic cardiomyopathy. Sixty-four percent of the subjects who completed our study protocol had echocardiographic evidence of HCM. The observed HCM was transient in nature, with resolution occurring uniformly by the third to fifth weeks of life.

While the majority of infants met the criteria for HCM by echocardiography, most remained asymptomatic and had normal measures of cardiac function (i.e. the ejection and shortening fractions). One of the subjects had symptoms consistent with congestive heart failure manifested by pulmonary edema and increased left atrial size with clinical signs of decreased cardiac output. Another subject who did not complete the study protocol died as a result of complications of prematurity (respiratory disease as well as interventricular hemorrhage). However, an echocardiogram did demonstrate hypertrophic chances consistent with HCM, in addition to diastolic dysfunction and pulmonary vascular congestion. While this subject was not included in the data analysis, this indicates that the HCM that develops in many of these premature infants may have a significant clinical impact.

A similar case report that supports our data was published by Gill et al in 1996.[11] These authors reported two extremely low birth weight infants who developed HCM as an iatrogenic complication of the concurrent therapeutic administration of glucocorticoid and insulin. Both infants developed symptomatic cardiac changes associated with marked myocardial hypertrophy, left ventricular outflow obstruction, and mitral valve dysfunction. There was no family history of HCM in either infant. As in our study, in

both of Gill's patients the HCM resolved completely on cessation of therapy. The authors postulated that insulin and dexamethasone acted synergistically to produce myocardial changes and recommended caution when treating glucocorticoid-induced hyperglycemia with insulin infusion, as the combination may induce a hypertrophic obstructive cardiomyopathy.

Previous data have demonstrated that transient HCM can be a rare sequela of both glucocorticoid and insulin excess.[11,13,14,19,21,23] We propose that the hyperinsulinemia in premature infants can produce hypertrophy and hyperplasia of immature myocardial cells in a manner similar to the fetus of a diabetic mother. The three therapies we specifically followed during the course of the study could all lead to hyperinsulinemia individually. When these therapies are combined, as is common in these very sick infants, they may act synergistically to induce hyperinsulinemia. Hyperalimentation, or total parenteral nutrition, is extremely rich in glucose, as this is the main source of caloric intake for these infants. High serum glucose levels directly stimulate pancreatic secretion of insulin, and may lead to hyperinsulinemia. Dexamethasone, a glucocorticoid, is known to induce peripheral insulin resistance and stimulate gluconeogenesis, and thereby lead again to hyperglycemia and hyperinsulinemia. The third therapy we analyzed was the exogenous infusion of insulin, a therapy which is employed when infants are not able to maintain euglycemia with the high doses of glucose contained in their parenteral nutrition. It is clear that an insulin infusion could in itself lead to high circulating levels of insulin, and directly act on the myocardial cells to cause hypertrophy.

Our results show that there is a corresponding transient relative increase in serum insulin levels in these premature infants that occurs during the second week of life. The

rise and fall of insulin levels corresponds in onset and duration to the development of HCM. This finding is analogous to the mechanism which explains the development of HCM in the infant of the diabetic mother. As in infants of diabetic mothers, the relative hyperinsulinemia in our subjects was transient and resolved by the third week of life.

It is interesting to note, however, that the relative increase in serum insulin levels occurred in both the subgroup of infants who developed echocardiographic evidence of HCM and those who did not develop HCM. This indicates that not all of our study subjects were susceptible to developing the disease. We hypothesize that these results indicate that there is a "window" of vulnerability in the myocardium of premature infants during which it becomes susceptible to the anabolic and metabolic effects of insulin at a particular stage of development. The subjects who developed HCM had an average gestational age of 27 weeks, two full weeks greater than those subjects who did not develop HCM. We propose that infants born at 24 to 25 weeks do not have a *developmentally vulnerable* myocardium two weeks postnatally when the peak in insulin levels occurs. Furthermore, we believe that HCM was not observed in these infants at four to five weeks of age (gestational equivalent of 28 to 29 weeks) due to resolution of the hyperinsulinemia. We believe that for HCM to develop in premature infants *both* high levels of insulin *and* a developmentally vulnerable myocardium are necessary. Therefore, our results indicate that although all premature infants become relatively hyperinsulinemic, only those who fall within this time window will be vulnerable to developing HCM.

Clinical experience at fetal cardiovascular centers suggests that the occurrence of HCM in infants of diabetic mothers is a third trimester phenomenon, beginning on

average between weeks 26 to 28 of gestation. This also coincides in time with the development of the fetal pancreas and significant production of insulin which occurs around the 20th week of gestation.[26] HCM is not observed until the pancreas is functional, since it has been well established that high levels of insulin are required for myocardial hypertrophy to occur. These observations again correspond to the window of time during which our study subjects developed HCM postnatally. Again, both for premature infants and for the fetus of the diabetic mother, we believe that it is during this time period that the myocardium is exposed to high circulating levels of insulin, resulting in hypertrophy of the myocardium. Thus our observations support the theory of a window of vulnerability when the developing myocardium is susceptible to the effects of hyperinsulinemia.

Initially we expected that the hyperinsulinemic effects of the three therapies we studied would be cumulative, that is the more therapies the infants received, the more hyperinsulinemic they would become, and therefore, the greater the incidence of HCM. However, this did not prove to be the case. While two of the eleven infants (18%) received all three therapies (hyperalimentation, dexamethasone, and exogenous insulin infusion), the change in septal thickness from baseline was actually less than in those who received hyperalimentation alone or hyperalimentation as well as dexamethasone. These two infants were among the smallest and gestationally immature of the study subjects. In fact it was those infants who received only hyperalimentation who developed the greatest change in thickness of the interventricular septum.

It is interesting to note, however, that the levels of relative hyperinsulinemia that occurred during the second week of life did correlate with our initial hypothesis. While

all three treatment groups showed a relative increase in insulin levels from baseline at week two of life, it was the infants who received all three therapies (hyperalimentation, dexamethasone, and insulin infusion) who had the highest peak levels of insulin. These infants, however, had the lowest incidence of HCM, as compared to the infants who received only one or two of these therapies in the intensive care unit (hyperalimentation and/or dexamethasone). However, the treatment groups were too small to allow for statistically significant measurements.

In order to explain these findings, we propose that the infants who developed HCM were a few weeks older in gestation, and therefore were a bit "healthier" than the even younger and more developmentally immature premature infants who tended to be more ill and require multiple therapies for survival. This again supports our theory that HCM only develops if the premature myocardium is exposed to high levels of insulin during a critical window of time during which it becomes vulnerable.

Prior investigators have reported an association between the development of HCM in newborns with bronchopulmonary dysplasia (BPD) and treatment with dexamethasone to accelerate ventilatory weaning. There are two issues to be dealt with. The first is the issue of systemic hypertension as a cause of the myocardial hypertrophy seen in patients with BPD, since glucocorticoids have been reported to lead to hypertension. Greengough found a direct relationship between the use of dexamethasone and an increase in systolic blood pressure in preterm infants with chronic lung disease.[24] However, both Brand[21] and Werner[23] studied the use of dexamethasone in premature infants and found that a causal relationship was unlikely. The patients in Brand's study had documented normal daily blood pressure measurements. In the

Werner study, he found a transient increase in heart rate and mean arterial blood pressure in premies treated with dexamethasone. However, Werner concluded that systemic hypertension was unlikely to be the cause of the observed HCM as the hypertrophy of the myocardium was felt to be out of proportion to the increase in blood pressure. Brand speculated that glucocorticoids result in hyperglycemia and hyperinsulinemia, and that it was this hyperinsulinemia which induced myocardial hypertrophy.

In our study, we followed daily blood pressure measurements in all subjects and there was no evidence of hypertension, regardless of the use of corticosteroids. Only one infant had a single daily systolic blood pressure greater that 90 mm Hg. Therefore, we cannot invoke systemic hypertension as a mechanism of left ventricular hypertrophy in these subjects.

Secondly, investigators have suggested that hypertension may be associated with chronic lung disease itself, as hypoxia and hypercarbia lead to stimulation of arterial chemoreceptors and lead to an increase in systemic vascular resistance.[25] Again, our patients had no evidence of developing hypertension. Moreover, in our study, HCM was observed in both infants who developed BPD and those who did not, as well as those who received dexamethasone and those who did not. In Brand's study, radiologic evidence of BPD persisted after the discontinuation of dexamethasone, while the resolution of their HCM corresponded in time to the discontinuation of the drug. Therefore, it seems unlikely that the cause of the observed HCM can be attributed to chronic lung disease and chronic hypoxia.

In conclusion, our results show that some premature infants develop a transient acquired hypertrophic cardiomyopathy after birth. We believe that the metabolic

environment of the premature infant is characterized by a period of transient hyperinsulinemia. This, coupled with the vulnerability of the immature myocardium, can lead to the development of HCM. We postulate that this process is analogous to the mechanism of HCM in the fetus of the diabetic woman. In both, high glucose levels lead to high insulin levels, and in both groups, the HCM resolves with the resolution of the hyperinsulinemia. The development of HCM in premature infants can be asymptomatic, or may lead to significant symptomatology including cardiopulmonary distress.

Further studies will focus on how the development of this hypertrophic cardiomyopathy can be modulated, perhaps by altering current management practices in the extremely premature infant and thereby decrease the occurrence of HCM and its subsequent morbidity and mortality. The findings of this study are previously unreported and may have important implications for the management practice of the premature infant.

Appendix A

White's Classification of Diabetes in Pregnancy
(from the American College of Obstetrics and Gynecology, 1986)

Class A: Gestational Diabetes
A1: Requiring insulin
A2: Not requiring insulin
Class B: Diabetes of the adult. Onset after age 20, lasting < 10 years
Class C: Diabetes developing before age 20, or > 10 years duration
Class D: Diabetes developing before age 10, or > 20 years duration
Class E: Any age/duration, plus calcified limb or pelvic vessels
Class F: Any age/duration, plus nephropathy
Class R: Any age/duration, plus retinopathy
Class RF: Any age/duration, plus nephropathy and retinopathy
Class H: Any age/duration, plus atherosclerotic heart disease
Class T: Any age/duration, plus renal transplant

Appendix B: Definition of Echocardiographic Parameters

Ejection Fraction (EF):

This gives a global impression of LV function, and is calculated by measuring the change in ventricular volumes between systole and diastole. It is stroke volume divided by the total end-diastolic volume:

EF = (EDV - ESV)/EDV

Where EDV = end diastolic volume

ESV = end systolic volume

EDV – ESV = stroke volume

Measurements of distance are converted to estimates of volume (cm^3) by the Tiecholz modified formula:

Volume = $(7.0 \times D^3)/(2.4 + D)$

where D = measured chamber diameter

Normal values for infants are between 55% and 80%.

Circumferential Shortening Fraction of the LV (SF):

This represents a change in the LV diameter in the short axis that occurs with systole.

%SF = (LVDD - LVSD)/LVDD x 100

where LVDD = left ventricular diastolic dimension

LVSD = left ventricular systolic dimension

The normal mean value is 36%, and the normal range in children and adults is 28% to 44%. This is independent of age and heart rate, but is dependent on both preload and afterload.

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